

BIOBEHAVIORAL PAIN RESEARCH

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National Institute of Nursing Research (NINR)

(<http://www.nih.gov/ninr>)

National Institute on Aging (NIA)

(<http://www.nia.nih.gov/>)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

(<http://www.niams.nih.gov/>)

National Cancer Institute (NCI)

(<http://www.nci.nih.gov/>)

National Institute of Child Health and Human Development (NICHD)

(<http://www.nichd.nih.gov/>)

National Institute of Dental and Craniofacial Research (NIDCR)

(<http://www.nidcr.nih.gov/>)

National Institute on Drug Abuse (NIDA)

(<http://www.nida.nih.gov/>)

National Institute of Mental Health (NIMH)

(<http://www.nimh.nih.gov/>)

National Institute of Neurological Disorders and Stroke (NINDS)

(<http://www.ninds.nih.gov/>)

National Center for Complementary and Alternative Medicine (NCCAM)

(<http://nccam.nih.gov/>)

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THIS PA CONTAINS THE FOLLOWING INFORMATION

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This program announcement replaces [PA-99-021](#), which was published in the NIH Guide on November 27, 1998.

PURPOSE OF THIS PA

The purpose of this biobehavioral pain research program announcement (PA) is to inform the scientific community of the interests of the various institutes at the National Institutes of Health (NIH) and to stimulate and foster a wide range of basic and clinical studies on pain as they relate to the missions of these Institutes.

Applications are encouraged to study individual differences in pain responses that may be due to factors such as genetic differences, endocrine activity, neural activity, immune function, psychological state, developmental stage, cognitive capacity, disability state, age, gender, social context and cultural background. The pain experience needs to be examined at all levels of research including the gene, molecule, cell, organ, and individual with the goal of developing biobehavioral interventions to manage or prevent pain.

RESEARCH OBJECTIVES

Pain is a critical national health problem. It is the most common reason for medical appointments, nearly 40 million visits annually, and costs this country over \$100 billion each year in health care and lost productivity. Pain has a profound effect on the quality of human life. In addition to possible deleterious effects on immune function, pain can cause disruptions in sleep, eating, mobility, and overall functional status. In the hospitalized patient, pain may be associated with increased length of stay, longer recovery time, and poorer patient outcomes, all of which have health care quality and cost implications.

Progress is being made in understanding the neuroanatomical pathways and the neurophysiological and neurochemical mechanisms involved in pain. However, understanding the subjective pain experience in individuals presents unique scientific challenges. Even though the basic physiology may be similar, people react in very different ways, perhaps due to genetic differences, endocrine activity, neural activity, immune function, stress, psychological state, developmental stage, age, gender, and cultural background. Thus, the pain experience needs to be examined at all levels of basic, clinical and biopsychosocial research with attention to the gene, molecule, cell, organ, and individual, including the individual as a member of a socio-cultural context. The goal of increased understanding of the pain experience is to develop biobehavioral interventions to manage or prevent pain.

Since 1994, NIH has been developing a research agenda dedicated to the identification of research needs from a broad spectrum of the scientific community expert in pain research. At that time, ten NIH institutes sponsored a workshop, "Biobehavioral Pain Research: A Multi-Institute Assessment of Cross-Cutting Issues and Research Needs,"

under the aegis of the NIH Health and Behavior Coordinating Committee. More recently, several institutes and the FDA co-sponsored a State-of-the Science Conference on Pain, Depression and Fatigue in Cancer (2002) that reiterated the need for an ongoing research agenda that will improve both the assessment and management of pain – as well as its interactions with other symptoms. In the intervening years, a rich variety of research has occurred, but more needs to be accomplished.

The following topics and study areas are not intended to be comprehensive or exclusive. In virtually all areas of research, however, given the growing body of research demonstrating gender differences in the experience and treatment of pain, as well as the genetic, molecular and neurochemical basis of pain, researchers are strongly recommended to develop gender-based research designs and to propose gender-based hypotheses.

These pain research areas cut across Institutes and programs and should not be viewed as restricted to only one specific Institute. Current NIH referral guidelines will be used to assign grant applications to the most appropriate NIH Institute based on the scientific focus of the application.

The following topics and study areas are not intended to be comprehensive or exclusive:

Understanding Critical Interfaces Between Biology and Behavior

- o Explore the neural basis of pain perception.
- o Examine the neuroendocrine and immunological correlates of pain.
- o Investigate relationships between pharmacological and behavioral interventions, including both conventional and complementary and alternative medicine (CAM) therapies, to prevent pain.
- o Use neuroimaging to study structural and functional correlates of pain perception.
- o Explore developmental aspects of pain processing, in particular approaches that could have an impact upon the treatment of pain across the life span.
- o Identify genes relevant to pain and pain inhibitory mechanisms, such as those that may account for differences in pain experiences and responses to pain management.
- o Develop models for the use of gene therapy to reduce pain, including the targeting of neurons or glial cells within the CNS.
- o Examine the use of targeted neurotoxins to kill pharmacologically specific cells within the pain detection/modulation pathways (e.g. target c-fibers with VR-1's within the dorsal horn of the spinal cord).

Pain, Suffering, and Emotion

- o Explore basic mechanisms of the conscious perception of pain and the affective responses to pain.
- o Examine the relative importance of biological, behavioral, developmental, psychological, environmental, and sociocultural variables in explaining variations in the course of pain, pain perception, pain dysfunction, response to treatment and pain-expressive behaviors.
- o Clarify the relationships among a variety of emotional states (e.g., anger, fear, anxiety and depression), which are associated with acute and chronic pain conditions, and determine how these cognitive states modify the experience of pain and treatment outcomes.
- o Develop reliable and valid measures and strategies for predicting and intervening with persons simultaneously afflicted with pain and depression, based upon knowledge of the relationship between biological factors, characteristics of pain (e.g., location, quality, timing), environmental circumstances, and psychosocial characteristics.

Pain and Behavior

- o Explore the sensory, cognitive, and affective aspects of acute and chronic pain across the lifespan.
- o Elucidate the interaction of biological markers, central nervous system mechanisms, and drug, behavioral, and CAM interventions.
- o Develop methods for assessing relative contributions of biological, psychological, behavioral, and environmental predictors of the course of pain, pain dysfunction, and response to treatment for pain in defined problem areas.
- o Examine addiction risk in patients taking controlled drugs for pain; the role of tolerance, addiction and dependence in the consumption of these drugs; and implications of long-term use in noncancer disease states.
- o Explore the use of virtual reality technologies as distractors/relaxers in the treatment of various types of pain (e.g., burn pain, dental pain).

Behavior-Related Interventions

- o Evaluate research strategies to integrate medical, rehabilitation, nursing, dental, neurological, pharmacological, psychosocial, behavioral, and CAM treatments for pain problems. Compare the relative effectiveness of each mode of treatment, and combined treatments, and their potentiating effects on multiple outcomes. These outcomes include

pain along with fatigue, sleep deprivation, physical functioning, and/or psychological functioning. The impact of the treatment(s) upon health care utilization and costs may also be examined in light of the physical and psychological outcomes.

- o Develop and refine biobehavioral techniques for optimizing adherence to pain management. Identify and consider barriers to adherence to pain management.
- o Conduct research on the mechanisms and process variables that are responsible for the efficacy of behavioral interventions. This research includes studies to understand better the effect of patients' expectations and beliefs, psychophysiological states (e.g., anxiety, relaxation, stress), adherence, and specific cognitive (e.g., imagery) and sociocultural (e.g., support systems) components in behavioral interventions.
- o Determine which behavioral treatments are most effective for specific subgroups of patients differentiated by factors such as age, developmental stage, gender, race, ethnic group, level of dysfunction, or psychosocial characteristics.
- o Conduct clinical trials of cognitive/behavioral pain control methods and combinations of medical, pharmacological, cognitive/behavioral, and CAM pain control methods. Examples of CAM therapies for pain control include, but are not limited to, massage, spinal manipulations, acupuncture, yoga, and meditation.
- o Establish dose-response curves for biobehavioral interventions.
- o Test interventions to improve health care practice in such areas as pain assessment, identification of barriers to pain management, analgesic management, pain prevention, and rehabilitation. Attention should be paid to the cultural competence of interventions.

Commonalities and Differences in Pain Expression, Experience, and Treatment

- o Study cognitive factors in the experience of pain, disability, and pain behaviors across disorders, including such factors as self-efficacy, perceived control, and pain beliefs.
- o Establish the biological/organic, psychosocial, and environmental factors that may cause progression from acute pain to chronic pain and then to a chronic pain-related disability.
- o Refine existing techniques for measuring pain and develop new techniques that are disease- and outcome-specific for different populations.
- o Determine the supraspinal mechanisms of pain modulation, determine the effects of specific pain treatments on these central nervous system processes, and apply new findings on CNS plasticity to the understanding of pain.

- o Examine the interrelationships between pain and other symptoms and comorbidities (e.g., fatigue, sleep alterations, nausea, vomiting, anxiety, mood disorders, physical deconditioning, stress).

Pain in Diverse and other Special Populations

- o Test culturally sensitive approaches to pain assessment and management, including appropriate methods for translation of the instruments into other languages and validation among speakers of languages other than English. Instrument development and validation among persons of various literacy levels and users of dialects other than standard English is also of interest.

- o Develop and test biobehavioral pain interventions for persons of various ethnic minority groups (including immigrants and refugees), either as a unique study or comparing interventions and outcomes across populations.

- o Investigate pharmacotherapies and biobehavioral pain management for special populations including infants, children, elderly, cognitively impaired, disabled, chronically and terminally ill, substance abusers (especially those with pain disorders), and patients with psychiatric diagnoses.

- o Investigate the prevalence and effectiveness of the use of complementary and alternative therapies for pain treatment in diverse populations such as ethnic minority groups, the elderly, the terminally ill, patients with HIV-AIDS and patients with other acute and chronic illnesses that are associated with pain.

- o Determine effective biobehavioral interventions for HIV- and AIDS-related pain and explore alterations in nociceptive mechanisms and pain perception. Pain prevalence, scope and severity of pain in the HIV-infected, and variations in nociceptive mechanisms depending on primary HIV/AIDS treatment regimen are also of interest.

- o Elucidate the interaction of pharmacotherapies and behavioral treatments with anti-retroviral treatment in HIV-infected persons.

- o Investigate the roles of sleep and circadian variation in the precipitation and modulation of pain in populations who have special rest - activity needs such as infants, children, elderly, pregnant women, night-shift workers. This research could include studies of the effect of pain and its pharmacological treatment on sleep and daytime alertness, as well as the effects of disturbed sleep on pain and pain perception. Studies of seasonal and other variations are also appropriate.

- o Test and evaluate pharmacotherapies, behavioral, and CAM treatments in patients with current and past histories of addiction, including infants born to drug-, alcohol-, and tobacco-dependent mothers.

- o Investigate the effectiveness of biobehavioral pain management in terminally ill and dying patients.
- o Conduct research on co-morbid mental disorders and pain, including descriptive studies of risk and protective processes as well as interventions aimed at relieving adverse consequences associated with co-morbid mental disorders and pain.
- o Study the interrelationship of Axis II, as well as Axis I, psychiatric disorders (e.g., borderline personality, histrionic, antisocial) and chronic pain, and relate these findings to pharmacological and behavioral therapies.
- o Explore the mechanisms that underlie gender differences in the pain response, e.g., genetic, molecular, hormonal, immunological, and, neurochemical.
- o Explore the role of the menstrual/estrus cycle on the pain experience, e.g., pain perception, pain threshold, development of chronic pain, and pain management.
- o Investigate biobehavioral approaches to managing pain associated with acute and chronic illness such as arthritis, fibromyalgia, cancer, diabetes, sickle cell disease, low back pain, headaches, temporomandibular disorders, and other orofacial pain conditions.

MECHANISMS OF SUPPORT

This PA will use the NIH R01 and R21 award mechanisms. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project. The objective of the R01 mechanism is to support a discrete, specified circumscribed project. The objective of the exploratory/developmental mechanism (R21) is to encourage applications from individuals who are interested in testing innovative or conceptually creative ideas that are scientifically sound and may advance our understanding of biobehavioral pain research. Investigators are encouraged to explore the feasibility of an innovative research question or approach that will provide a basis for future research projects. Exploratory/developmental grants (R21) are limited to 2 years of support with a combined budget for direct costs of up \$275,000 for the two year period. For example, the applicant may request \$100,000 in the first year and \$175,000 in the second year. The request should be tailored to the needs of the project. Normally, no more than \$200,000 may be requested in any single year. Please see the NIH-wide R21 program announcement (PA-03-107) (see <http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html>). Please see the "Submitting an Application" section for more details.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see <http://grants.nih.gov/grants/funding/modular/modular.htm>). Specifically, if you are submitting an application with direct costs in each year of \$250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications. This program does not require cost sharing as defined in the current NIH Grants Policy Statement at http://grants.nih.gov/grants/policy/nihgps_2001/part_i_1.htm.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

- o For-profit or non-profit organizations
- o Public or private institutions, such as universities, colleges, hospitals, and laboratories
- o Units of State and local governments
- o Eligible agencies of the Federal government
- o Domestic or foreign
- o Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into two areas: scientific/research, and financial or grants management issues:

- o Direct your questions about scientific/research issues to:

Dr. Martha Hare
Office of Extramural Programs
National Institute of Nursing Research
6701 Democracy Blvd, Room 710, MSC 4870
Bethesda, MD 20892-4870
Telephone: (301) 451-3874
FAX: (301) 480-8260
Email: Martha.hare@nih.gov

Dr. Judith A. Finkelstein, Ph.D.
Head, Office of Nutrition
Director, Sensory/Motor Disorders of Aging Program
National Institute on Aging
Neuroscience and Neuropsychology of Aging
Gateway Building, Suite 350
7201 Wisconsin Avenue
Bethesda, MD 20892-9205

Telephone: (301) 496-9350
FAX: (301) 496-1494
Email: jfl19k@nih.gov

Dr. Deborah N. Ader
Behavior and Prevention Research Program Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza, Suite 800
Bethesda, MD 20892-4872
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: aderd@mail.nih.gov

Dr. Paige A. McDonald
Program Director, Basic Biobehavioral Research Branch
Behavioral Research Program
Division of Cancer Control and Population Sciences
National Cancer Institute, NIH, DHHS
6130 Executive Boulevard, MSC 7363
Executive Plaza North, Room 4062
Bethesda, MD 20892-7363
Telephone: (301) 496-8776
FAX: (301) 435-7547
Email: mcdonalp@mail.nih.gov

Dr. Louis Quatrano
Behavioral Sciences and Rehabilitation Engineering
National Institute of Child Health and Human Development
6100 Executive Blvd., 2A03, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 402-4221
FAX: (301) 496-0832
E-mail: quatranl@exchange.nih.gov

Dr. Patricia Bryant
Clinical, Epidemiology, and Behavioral Research Branch
Division of Population and Health Promotion Sciences
National Institute of Dental and Craniofacial Research
Bldg 45, Room 4AS-43A
Bethesda, MD 20892-6402
Telephone: (301) 594-2095
FAX: (301) 480-8322

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Dr. Dave Thomas
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6001 Executive Blvd.
MSC 9555
Bethesda, MD 20892
Telephone: (301) 443-6975
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Email: dt78k@nih.gov

Dr. Peter Muehrer
Chief, Health and Behavioral Science Research Branch
Division of Mental Disorders, Behavioral Research, and AIDS
National Institute of Mental Health
National Institutes of Health
6001 Executive Boulevard, MSC 9615
Room 6189
Bethesda, MD 20892-9615
Telephone: (301) 443-4708
FAX: (301) 480-2920
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Dr. Linda Porter
Systems and Cognitive Neuroscience
National Institute of Neurological Disorders and Stroke
6001 Executive Blvd., Room 2113
Bethesda, MD 20892-9521
Rockville, MD 20852 (Courier)
Telephone: (301) 496-9964
FAX: (301) 402-2060
Email: lp216a@nih.gov

Dr. Nancy Pearson
Program Officer
Neuroscience, Mental Health, NRSA Training Programs
National Center for Complementary and Alternative Medicine
6707 Democracy Boulevard, Room 106, MSC 5475
Bethesda, MD 20892-5475
Telephone: (301) 594-0519
FAX: (301) 480-3621
Email: pearsonn@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Diane Drew
Office of Grants and Contracts Management
National Institute of Nursing Research
6701 Democracy Blvd, Room 710, MSC 4870
Bethesda, MD 20892-4870
Telephone: (301) 594-2807
FAX: (301) 451-5651
Email: diane.drew@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at <http://grants.nih.gov/grants/funding/phs398/phs398.html> in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTAL INSTRUCTIONS: All instructions for the PHS 398 (rev. 5/2001) must be followed, with these exceptions:

o Research Plan

Items a - d of the Research Plan (Specific Aims, Background and Significance, Preliminary Studies, and Research Design and Methods) may not exceed a total of 15 pages. No preliminary data is required but may be included if it is available. Please note that a Progress Report is not needed; competing continuation applications for an exploratory/developmental grant will not be accepted.

Appendix. Use the instructions for the appendix detailed in the PHS 398 except that no more than 5 manuscripts, previously accepted for publication, may be included.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at <http://grants.nih.gov/grants/dates.htm>. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:

Applications requesting up to \$250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in \$25,000 modules. Section C of the research grant application instructions for the

PHS 398 (rev. 5/2001) at <http://grants.nih.gov/grants/funding/phs398/phs398.html> includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING \$500,000 OR MORE PER YEAR:

Applications requesting \$500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application.

Applicants requesting more than \$500,000 must carry out the following steps:

- 1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;
- 2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,
- 3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html>.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be mailed on or before the receipt dates described at <http://grants.nih.gov/grants/funding/submissionschedule.htm>. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (<http://www.csr.nih.gov/refrev.htm>) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- o Receive a written critique
- o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
- o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

- o Significance
- o Approach
- o Innovation
- o Investigator
- o Environment

The scientific review group will address and consider each of these criteria in assigning the application's overall score, weighting them as appropriate for each application. The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

SIGNIFICANCE: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

The NIH R21 exploratory/developmental grant is a mechanism for supporting novel scientific ideas or new model systems, tools or technologies that have the potential to significantly advance our knowledge or the status of health-related research. Because the research plan is limited to 15 pages, an exploratory/developmental grant application need not have extensive background material or preliminary information as one might normally expect in an R01 application. Accordingly, reviewers will focus their evaluation on the conceptual framework, the level of innovation, and the potential to significantly advance our knowledge or understanding. Reviewers will place less emphasis on methodological details and certain indicators traditionally used in evaluating the scientific merit of R01 applications including supportive preliminary data. Appropriate justification for the proposed work can be provided through literature citations, data from other sources, or, when available, from investigator-generated data. Preliminary data are not required for R21 applications.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL CONSIDERATIONS

DATA SHARING: The adequacy of the proposed plan to share data.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

- o Scientific merit of the proposed project as determined by peer review
- o Availability of funds
- o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. <http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>

MONITORING PLAN AND DATA AND SAFETY MONITORING BOARD: Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html>); a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:

The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at

<http://grants.nih.gov/grants/funding/children/children.htm>.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT

PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html>.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at <http://stemcells.nih.gov/index.asp> and at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html>. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see <http://escr.nih.gov>). It is the responsibility of the applicant to provide the official NIH identifier(s) for the hESC line(s) to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (<http://www.hhs.gov/ocr/>) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html>.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-

led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at <http://www.health.gov/healthypeople>.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at <http://www.cfda.gov/> and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at <http://grants.nih.gov/grants/policy/policy.htm>

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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